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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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Cadmium: Position Document 1

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I. Background

A. General Chemistry

Cadmium occurs naturally, belongs to Group IIB in the periodic table of elements and has a molecular weight of 112.4. It constitutes 0.0001% of the earth's crust and is found primarily as the mineral Greenockite (cadmium sulfide), which is not mined commercially but is extracted during zinc and lead mining operations. Electrolysis of smelted ore yields 99.9% pure metallic cadmium. The melting point and boiling point of elemental cadmium are 321^{o} and 765^{o}C, respectively; its density is 8.642 g/ml (1).

B. Production

About 12,000 pounds of pesticidal cadmium were produced in 1975. The production for 1976 is reported to have exceeded 20,000 pounds; that for 1977 is estimated to be as high as 40,000 pounds.

Section 7(c) of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires manufacturers and formulators to submit information on production, distribution, and sales of pesticidal cadmium compounds. Under Section 7(d) and 10 of FIFRA this information is considered confidential and may not be made available to the public.

The information is available to the Administrator in a confidential appendix to this report.

World-wide production of cadmium was reported as 17 million kilograms for 1975. To supplement domestic cadmium production, the United States imported 2.5 million kilograms in 1975 to meet an industrial demand of 5.6 million kilograms. Manufacture of cadmium pesticides accounted for less than 0.1% of the total amount of cadmium used in the United States (2).

C. Registered Uses

Pesticidal cadmium compounds are registered as fungicides in sprays, dusts, and granular powders for application on ornamental turf, professional turf, and home lawns at a rate of 0.2 to 1.0 ounce of actual cadmium per 1000 square feet. Application rates vary depending on whether cadmium is applied alone or in combination with other fungicides.

There are 35 Federally registered cadmium products and one State registration for which Federal registration is pending (Table 1).

Table 1. Federal Registrations and Registrants of Pesticidal Cadmium Compounds

Compound	Registrations (number)	Registrants (number)
Cadmium chloride	25*	22
Cadmium carbonate	4	2
Cadmium sebecate	2	2
Cadmium succinate	3	3
Anilocadmium dilactate	1	1

* There is one pending Federal registration.

D. Alternative Pesticides

Alternative pesticides registered for use as fungicides on turf include dyrene, folpet, thiram, the ethylenebisdithiocarbamates, parachloronitrobenzene, captan, and benomyl. Of these, benomyl, the ethylenebis-dithiocarbamates, and parachloronitrobenzene are themselves under review by the Office of Special Pesticide Reviews.

E. Environmental Occurrence

1. Soil

Cadmium occurs in soil as a natural component, as a residue of fungicides applied directly to turf, and as a pollutant from industrial operations.

In soil samples taken from golf courses treated with cadmium fungicides, residues ranged from none detectable to 62.5 ppm, with a mean of 8.4 ppm. The greatest amounts were found in the top 4 inches of the soil, a fact that

indicates that cadmium does not migrate downward. Cadmium's translocation laterally through the soil is evidenced by its presence in the sediment of streams and ponds on the golf courses which have used cadmium pesticides. Half of the samples of sediment contained cadmium in amounts up to 94.4 ppm, with a mean of 1.5 ppm (3).

Industrial pollution from several sources deposits cadmium in the soil. Cadmium particulates in the air settle to the ground and add measurably to the amount of cadmium in soils. The use of landfills for repositories of sludge creates areas of abnormally high concentrations of cadmium. The effluent from sewage treatment facilities contains 22 to 57 metric tons of cadmium per year (4). The concentration of cadmium averaged 3 ppm in the liquid effluent and 12 ppm in the sludge (5).

The amount of cadmium in soils is relatively low in nonindustrialized areas. Des Moines, Iowa, had means of 0.89 and 0.28 ppm in the urban and suburban areas, respectively, in contrast to Pittsburgh, Pa., an industrial center, which had a mean of 1.21 ppm for urban and 0.90 ppm for suburban areas (6).

2. Air

The amount of cadmium in the air depends on the degree of industrialization in a particular area. In a 1969 survey, the concentration of cadmium in air ranged from 0.006 mg/m^3 in San Francisco,

Ca., to 0.036 mg/m^3 in St. Louis, Mo. The highest concentration recorded in the United States, 0.12 mg/m^3, was measured in 1964 in El Paso, Texas (7). A 1970 survey, although limited, confirmed the 1969 study (7). IARC reported that concentrations of cadmium worldwide averaged less than 0.003 mg/m^3 in rural areas but as much as 0.050 mg/m^3 in industrialized cities. In the vicinity of cadmium-emitting industries concentrations as great as 0.5 mg/m^3 were recorded (2).

3. Water

Once deposited in water, cadmium is freely mobile (7). In rural areas, most cadmium comes from naturally occurring sources. In urban areas, naturally occurring cadmium is augmented by cadmium from industrial and commercial sources. Data from the Office of Water Supply in EPA indicate that cadmium is present in drinking water in amounts ranging from 0.01 ppm, the limit of detection, to 0.7 ppm.

4. Food

Cadmium (0.01 to 0.2 ppm) has been detected in foods of all categories monitored by FDA in its Market Basket Survey. The highest amounts were generally found in leafy vegetables and canned foods (8). The cadmium found in leafy vegetables probably does not result from application of cadmium pesticides because such pesticides are not registered for use on food crops.

The high concentrations found in green plants probably result from translocation of cadmium from soil, which is fortified by small amounts of cadmium impurities contained in phosphate fertilizers (9) and by unabsorbed cadmium ingested by animals and eliminated and redeposited in the soil or landfill (7).

5. Other

Humans are also exposed to cadmium in cigarette smoke. The IARC reports that each cigarette contains 1.7 ug of cadmium, up to 10% of which can be absorbed through the lungs into the circulatory system. In one year, a moderate smoker (one pack per day) may increase his total body burden of cadmium by 0.5 mg (2).

6. Body Burden

The total body burden varies with country and occupation. To arrive at a general mean, IARC (2) discounted occupational exposures and calculated the daily intake of cadmium from all other sources (Table 2).

Table 2. Daily Cadmium Intake

Country	Cadmium (ug/day)
Czechoslovakia	60
Japan	47-59
US	4-92

Cadmium accumulates in sensitive target organs in which calcium has an important metabolic function. In the United States the average concentration of cadmium in the adult kidney was reported as 40 ug per gram wet weight, a value approximately one-half that for Japan (7).

Cadmium deposits in the body reach a maximum at about age 50 and thereafter decline logarithmically. The total body burden estimated at age 50 is 40 mg, the urinary excretion rate being less than 12 ug per liter of urine (10).

Once absorbed, cadmium is bound by metallothionein, a low molecular weight protein found in all organs associated with high concentrations of cadmium. Although metallothionein is thought to function in detoxifying or storing potentially toxic heavy metals, the amount of protection afforded is not known (7).

F. Toxicology

Cadmium has been the subject of a number of studies designed to identify and evaluate potential toxicological effects. These studies have used a variety of common cadmium compounds, some of which are not registered as pesticides. An EPA scientist at Research Triangle Park Laboratory advised the Cadmium Working Group that regardless of the cadmium salt used, the results observed can be attributed to the cadmium ion (11). Thus, the Cadmium Working Group has considered some studies which used cadmium compounds not registered as pesticides.

1. Human

Cadmium has been reported to affect many organ systems (7). A more detailed analysis of these effects in relation to exposure and dosage is addressed in Sections III and IV.

2. Wildlife

Data on the effects of cadmium to wildlife have not been reported in as much detail as the effects of cadmium on humans. A summary of some of the available data is presented below.

The LC_{50} for bluegills has been measured as 80 ug/liter in water hardness of 200 mg/liter. Higher concentrations of cadmum did not inhibit spawning of surviving fish, but newly hatched progeny were deformed (12).

A study of the toxicity of cadmium to brook trout reported an LC_{100} of 6.4 ug of cadmium per liter in water hardness of 44 mg/liter. A concentration of 3.2 ug/liter killed the males either before or just after mating. The number of surviving embryos was smaller at this dosage. At a concentration of 1.7 ug/liter cadmium had no apparent effect on the reproductive capacity of the males or females (13).

The 96 hour LC_{50} of cadmium for flagfish was reported as 2500 ug/liter in water hardness of 4 mg/liter. The mortality of fish exposed to lower amounts of cadmium (31 ug/liter and 16 ug/liter) for up to 60 days was greater than that of controls. Growth of the fish exposed to cadmium in these concentrations was also reduced (14).

In 3-week-old chicks cadmium (9.5 mg/kg) interfered with the normal intestinal absorption of iron, causing an anemic condition typical of that found in mammals chronically exposed to low amounts of cadmium (15).

Japanese quail fed cadmium (75 mg/kg/day) for 6 weeks after hatching experienced various adverse effects when other minerals were deficient in their diet. Birds fed a diet deficient in zinc developed testicular hypoplasia, and their growth was retarded. Diets deficient in iron produced anemia and bone marrow hyperplasia. In both cases the heart was hypertrophied within 2 weeks after the experiment began (16).

The LC_{50} for quail fed formulated cadmium succinate was reported as 1700 mg/kg; that for mallard ducks was 5000 mg/kg (17).

Since cadmium pesticides are not applied directly to water, the hazard to aquatic species from normal application of cadmium pesticides seems minimal. The limited use of cadmium on home lawns and golf turf suggests that hazard to avian or mammalian species from cadmium pesticides would be similarly unlikely. Therefore, the Working Group has concluded that none of the data concerning toxicity to wildlife are sufficient to meet the criteria of 40 CFR 162.11(a)(3)(i)(B) and 162.11 (a)(3)(ii)(c).

II. Regulatory History

Until 1968 cadmium compounds were registered both for use on turf and for limited use on food crops. Tolerances were established for these uses under the "no residue/zero tolerance" provisions of the regulations then in effect. After the U.S. Department of Agriculture discontinued the application of the "zero tolerance/no residue" principle, all registrations for the use of cadmium on food crops were cancelled by PR Notice 68-6, dated February 1, 1968, since data supporting finite tolerances were not submitted. The turf uses of cadmium were not affected by this notice.

The Administrator of EPA has placed a high priority on collection and review of data on cadmium (18). Many nonpesticidal uses of cadmium are subject to regulation under the Toxic Substances Control Act (TSCA) and regulatory action has been initiated under the Safe Drinking Water Act of 1974, which requires standards of purity in the Nation's drinking water supply. In its report to EPA the National Academy of Sciences recommended that the amount of cadmium in drinking water be limited to 10 ug/l (69). This standard was incorporated into the National Interim Primary Drinking Water Regulations which became effective on June 24, 1977 (70).

The National Cancer Institute is evaluating the oncogenicity of cadmium compounds injected into rodents.

The National Institute for Occupational Safety and Health (NIOSH) has recommended that occupational exposure not exceed 40 ug/m^3 per 10 hour day. NIOSH has also recommended that systems of medical examination, keeping medical records, sampling and analysis, area labeling, providing of protective clothing, training employees, and improving general work practices be used by industry (1).

III. Summary of Scientific Evidence to Support Rebuttable Presumption: Chronic Toxicity

40 CFR 162.11(a)(3) provides that a rebuttable presumption shall arise if a pesticide's ingredients, metabolites, or degradation products meet or exceed (i) acute toxicity risk criteria relating to hazards to humans, domestic animals, or wildlife, or (ii) chronic toxicity risk criteria relating to oncogenic, mutagenic, and delayed toxic effects in man or test animals, or relating to population reductions in nontarget organisms or fatalities to members of endangered species.

The Cadmium Working Group has concluded that pesticide products containing cadmium meet or exceed the chronic risk criteria relating to oncogenesis and mutagenesis. Certain uses of cadmium pesticides also meet or exceed the criteria relating to teratogenicity and fetotoxicity. Therefore, a presumption has arisen against all pesticides containing cadmium.

A. Oncogenic Effects

The Carcinogen Assessment Group (CAG) of EPA has reviewed laboratory studies on the oncogenic properties of cadmium administered orally and parenterally to animals and epidemiologic studies of humans exposed to cadmium by inhalation or dermal contact. The CAG concluded that (i) the number of tumors at sites removed from the site of injection increased significantly in animals injected with cadmium; (ii) significant increases in prostate cancer were found in persons occupationally exposed to cadmium; and (iii) chronic oral studies, although reported as negative by their authors, must be considered inconclusive because of protocol deficiences. The CAG also noted that some mutagenic actions of cadmium, including mammalian cellular transformations, have a high correlation with oncogenicity (19).

The CAG has considered all data bearing on the potential oncogenicity of cadmium regardless of the route of exposure. However, a rebuttable presumption on the basis of oncogenic effects arises only if such effects are observed in man or animals following oral, dermal, or inhalation exposure. The Working Group has concluded that the epidemiological data alone indicate that cadmium pesticides pose an oncogenic risk and are sufficient evidence to warrant a rebuttable presumption. The epidemiological studies are directly applicable to cadmium pesticide use since the routes of exposure in these studies (dermal and inhalation) are the same as the routes of exposure to cadmium pesticides.

Four occupational epidemiology studies (20,21,22 and 23) were reviewed by the CAG. In all of them, an association between prostate cancer and cadmium is suggested. In two of these studies, Kipling and Waterhouse (21) and Lemen et al. (22), the results obtained were statistically significant. The remaining two studies (20 and 23) suggest a correlation between cadmium exposure and excess prostate cancer mortality although no statistical analysis was completed. While these studies involved small numbers, the consistency of their findings raise a serious questions as to the relationship of cadmium exposure and prostate cancer.

Berg and Burbank (24) reported that the presence of cadmium (3 ug/liter) in the drinking water supplies of the United States was positively correlated with the incidence of cancer in those areas. Cancers for which there was positive correlation included cancer of the pharynx, esophagus, intestine, larynx, lung, and bladder. The authors did not include the incidence of prostatic cancer among their data. A second drinking water study also indicated that a high concentration of trace metals, including cadmium, was positively correlated with the incidence of cancer in Czechoslovakia (25).

Accordingly a presumption has arisen against cadmium pesticides on the basis of the oncogenic effects observed in epidemiological studies.

B. Mutagenic Effects

The potential mutagenic effects of cadmium have been described in several comprehensive reviews and papers which have been evaluated by Agency scientists. Their analysis concludes that "cadmium does show the potential of interferring with the genetic material in living organisms" (26) and that "there is supportive evidence that cadmium may cause DNA damage leading to point mutations" (27). The valid studies indicate that cadmium is a point (gene) mutagen and can cause chromosomal damage.

Primary damage to DNA by cadmium has been observed in *in vitro* mammalian cell systems, bacteria and yeast. Chinese hamster embryo cells underwent unscheduled DNA synthesis after exposure to cadmium chloride and cadmium acetate, indicating an attempt by the cell to repair DNA damage presumably caused by the cadmium (28). Cadmium chloride induced a statistically significant increase of mispaired nucleotides when added to the *in vitro* DNA synthesis system (29). Cadmium chloride produced mutant recombinants using the recombinant assay test system in strains of *Bacillus subtilis*. Cadmium nitrate, which is not registered as a pesticide, was negative (30).

Cadmium chloride produced abnormal mitotic and meiotic recombinations in yeast, *Sacharomyces cerevisiae*, indicating that cadmium is capable of producing potential heritable damage in eukaryotic cells (31).

Cultured human leukocytes were exposed to cadmium sulfide for 4 to 8 hours. Cells examined microscopically for chromosomal aberrations revealed chromatid breaks, isochromatid breaks, translocations, and dicentrics (32). Similar chromosomal aberrations were found in human leukocytes from persons diagnosed with Itai-Itai disease. In addition the frequency of these aberrations was statistically greater in the Itai-Itai patients than in normal persons serving as controls (33).

Cadmium is capable of penetrating germinal tissue barriers and causing direct chromosomal damage. In an *in vivo* germinal cytogenetics test female mice were treated with an acute dose of cadmium chloride (3 or 6 mg/kg) and sacrificed after stimulation of ovulation. When examined microscopically, oocytes of treated animals revealed numerical chromosomal anomalies including hypoploidy, hyperploidy and diploidy. No such effects were observed in untreated controls. Cadmium chloride also blocked development of metaphase I chromosomes in some of the animals and caused hemorrhaging of the ovaries (34).

Cadmium that penetrates the blood-testis barrier can affect development of mature sperm. When the rates of spermatogenesis in rats were measured at different times during development, more immature sperm cells were found after introduction of cadmium chloride than were found in controls. The rate of incorporation of radioactively labelled amino acid was also depressed, a fact that reflects a decreased rate of protein synthesis. The data also show a decreased fertility index for 50 days after the rats were injected intraperitoneally with cadmium at 1 mg/kg and then mated. After 50 days the fertility index returned to 80% of the initial levels (35). See also page 28 for additional gonadal effects.

The negative studies which were analyzed were either not sufficiently sensitive to mutagenicity for an accurate evaluation (36,37), lacked sufficient sample numbers (38), or were encumbered by other environmental factors which may have impacted on the stated results (39). A complete summary of all tests pertaining to mutagenicity is included in Table 3.

Table 3. Summary of Tests Pertaining to Mutagenicity

Test System	Genetic Effect	Presence (+) or Absence (-)	Appendix
	Systems in vitro		
Chinese Hamster Cells	Point mutation	+	28
Polynucleotides	Base mispairing	+	29
Human cells	Chromosomal damage	+	32
B. subtilis - Recombinant assay	Gene mutation	+	30
S. cerevisiae	Point mutation	+	31
	Systems in vivo		
Human	Chromosomal damage	+	33
Human	Chromosomal damage	-	38
Rat	Altered spermatogenesis	+	35
Mouse	Dominant lethal mutations	-	36
Mouse	Cytogenetic damage	+	34
D. melanogaster	Sex-linked recessive lethal	-	37
Mammals	Chromosomal abnormalies	-	34

This evidence is ample to meet the definition of "multitest evidence" required by 40 CFR 162.11. The Working group has concluded, therefore, that a presumption has arisen against all pesticides containing cadmium on the basis of their mutagenic effects.

C. Teratogenic Effects and Fetotoxic Effects

Many publications have reported that cadmium is a potent animal teratogen and fetotoxic agent. For the purpose of this document 24 papers were reviewed by Battelle Memorial Laboratories, Columbus, Ohio. Their analysis concluded that cadmium is teratogenic in rats, mice, and hamsters (40). None of the studies which were reviewed established a no observable effect level.

Cadmium is transferred across the placenta to the fetus (41). This fact is extremely important because it demonstrates that cadmium can act directly upon the embryo, as well as indirectly by inducing toxic effects in the mother, which in turn might affect development. Battelle reviewed the available evidence and concluded that cadmium is a fetotoxic agent and that it inhibits postnatal survival and breeding.

Unlike most other chronic effects which manifest themselves very slowly over long periods, teratogenic and fetotoxic effects can be induced by one exposure occurring at a critical time. The evidence suggests that cadmium may exert such effects regardless of it route of administration or the time during gestation at which it is given.

When cadmium was administered to mice on day 7 of gestation, the adverse effects included decreased weight, exencephalia, excessive nucleic acid synthesis, and decreased

growth of the brain (42). When cadmium was administered on days 14 to 17 of gestation, death of the embryo ensued attended by uterine hemorrhaging and other alterations in the vascular system (44). These data have been substantiated in a feeding study in which the death rates of the young and the production of runts of treated and control animals were significantly different. For lack of animals, the experiment was terminated with the F_2 generation (45).

In rats, the fetotoxic and teratogenic effects of cadmium (1.6 mg/kg in drinking water) included fetal mortality and decreased gross weight, hydrocephaly, cryptorchidism, hydronephrosis, and anophthalmia or microphthalmia (46). When rats were subcutaneously injected with cadmium (4 to 12 mg/kg), fetuses developed agnathia, cleft palate, and hypoplastic lungs (47). The differences in effects observed in these studies may be attributable to the different routes of administration and the days of treatment (gestation days 9 to 11 and 14 to 17, respectively).

In hamsters given cadmium intravenously (2 mg/kg given on gestation day 8) adverse effects included resorption of the fetus and formation of cleft palates and deformities in the primitive neural tube (exencephalia and microphthalmia) In another experiment, intravenous administration of cadmium at the same dose and time produced statistically significant gross malformations of the fore and hind limbs, including amelia, micromelia, and ectodactyly (48).

In a German study (41), women from three areas of differing degrees of industrialization were examined for cadmium levels in their placentas. Women in the most highly industrialized area, Rhine-Ruhr, had a mean level of 74.5 ug of cadmium in their placentas. This level was statistically higher than the two other lesser industrialized areas evaluated, Middle Frankonia (51.9 ug of cadmium) and Bavaria (55.1 ug of cadmium). This report did not evaluate the rate of miscarriage or the size of the children to assess any impact of cadmium on the pregnancy. However, another report stated that women occupationally exposed to cadmium did have abnormally small children (49). Because this study was not a controlled experiment, its data must be considered inconclusive.

Unlike the presumptions based on oncogenicity and mutagenicity, EPA regulations require that a presumption based on "other chronic effects" such as teratogenicity and fetotoxicity, must take into account human exposure in determining whether the criterion has been exceeded. The Working Group is unaware of any definitive data indicating the precise quantities of cadmium to which humans are exposed as the result of the use of cadmium pesticides. The Criteria and Evaluation Division (CED) of OPP has prepared a document titled "Preliminary Analysis of Human Exposure to Cadmium from the Use of Cadmium Turf Fungicide" (50). In the absence of empirical evidence regarding human

exposure, this analysis necessarily relies on certain assumptions, but its conclusions provide the best estimate available. The Working Group specifically solicits further exposure data, particularly from actual use.

In its analysis, the CED assumed that women of child-bearing age would only be exposed to cadmium pesticides from their use around the home. The professional use of cadmium pesticides on golf courses does not appear to result in significant exposure to women since only 6 of over 12,000 turf-maintenance supervisors are women (51). The CED document further assumes that as much as one pint of prepared cadmium spray could come in contact with the applicator during each use. Assuming 2% absorbtion to the sprays, the report concluded that an applicator could absorb as much as 0.8 mg of cadmium through dermal exposure to the sprays. Inhalation of a coarse water droplet was considered unlikely. In applying the dust a person could be exposed to as much as 0.8 mg of cadmium through combined dermal and inhalation exposure. The estimate assumes that normal clothing will limit dermal absorption to 0.5 mg and that the only inhalation exposure would result from the actual loading of the application equipment (0.3 mg of cadmium). Although cadmium pesticides are applied at most 12-14 times a year, only one exposure at a critical time is necessary to produce teratogenic and fetotoxic effects.

If a 60 kg woman were exposed to 0.8 mg of cadmium, she would receive a dose of 0.014 mg/kg. The Working Group does not consider the difference between this estimate of possible exposure and the lowest dosage which caused effects in the experimental studies great enough to ensure that no hazard will be posed to women that use cadmium pesticides. The difference becomes especially important since none of the studies reviewed demonstrated a no-effect level.

For the reasons stated above the Working Group concludes that the risk criterion is met and that a presumption based on teratogenicity and fetotoxicity has arisen against cadmium pesticides registered for home use.

IV. Other Effects

Cadmium is known to cause a number of adverse health effects in humans who have been exposed for relatively long periods of time to relatively high levels of cadmium. In addition, laboratory studies indicate that cadmium can cause a variety of adverse effects in test animals exposed to cadmium by several routes of exposure. However, it does not appear that any of the effects described below will occur at levels to which humans might reasonably be anticipated to be exposed from the use of pesticides, taking into account ample margins of safety. Moreover, the frequency and duration of exposure required to produce these effects does not seem comparable to exposure from application of

cadmium pesticides. For these reasons the Cadmium Working Group has concluded that none of the effects discussed below warrants issuance of a presumption at this time.

A continuing effort will be made by the Working Group to collect additional data from all sources, including other regulatory groups and scientific organizations to determine if, with additional data, the criteria expressed in 40 CFR 162.11 are met for cadmium pesticides. In addition, the Agency, with the assistance of the United States Golf Association, has initiated a study of professional applicators of cadmium pesticides to determine if such persons exhibit signs of proteinuria, a condition often associated with excessive cadmium exposure and believed to be a possible indication of other adverse effects. If any of the data received or generated indicates potential risk, the Agency will consider additional regulatory action, including the issuance of a supplemental Notice of Rebuttable Presumption Against Registration.

The Working Group recommends solicitation of any additional information on the cadmium effects described in the following sections or any other effects which may be attributable to pesticidal cadmium.

A. Effects on the Lungs

In humans, acute effects of doses of cadmium smaller than the estimated LD_{50} (approximately 2400 mg-min/m^3) manifest themselves within 4 to 10 hours after exposure.

Nonlethal effects of such doses in fumes or aerosols usually consist of pulmonary edema and interstitial pneumonitis from which damage in the form of perivascular and peribronchial fibrosis results (1,7).

Emphysema has been observed in humans following lengthy exposure to low doses of cadmium (1,7). Animal studies indicated that cellular changes typical of early stages of emphysema occur in rats given 17.2 ug/ml of cadmium in water daily for 6 to 41 weeks (52). Emphysema was induced in rats and guinea pigs by daily intratracheal administration of cadmium (2.5 mg/kg) for 4 and 7 months, respectively (53). A single intratracheal dose of cadmium chloride in an aerosol (9 mg/kg) induced preliminary symptoms of emphysema (54). However, an aerosol particle is much smaller and more readily absorbed than the coarse water droplet which would be encountered in the application of cadmium pesticides.

B. Effects on the Kidneys

Industrial workers accidentally inhaling high levels of cadmium fumes have suffered from acute renal necrosis (55). Temporary proteinuria has developed in humans exposed to subacute amounts cadmium for short periods (56), and renal failure is believed to have caused the death of a worker exposed to unmeasured levels of cadmium (20). Renal lesions, particularly formation of fatty bodies and degeneration of tubules, develop in animals exposed to large amounts of cadmium (1).

The effects of chronic exposure to cadmium are primarily proteinuria, glucosuria, excretion of amino acids in the urine, and decreased renal function (1). A specific protein, B-2 microglobulin, has recently been identified in the urine of Swedish workers and Japanese farmers exposed to cadmium (67).

When cadmium was given to rats in drinking water (0.2, 2.0, 20 and 200 ppm) changes (either constriction or dilation) to the renal arterial blood vessels resulted. These changes were not dose dependent, but seemed to be related to the dietary calcium levels. Rats with normal calcium levels in their diet experienced less alteration to the diameter of the blood vessels examined than those with low calcium levels (57).

Rats given cadmium in their drinking water (10, 50 and 300 ppm) for up to 40 weeks had an increased number of lysosomes in the kidney tubular epithelium. This increase was postulated by the authors to be related to the degeneration of renal tubules as previously theorized by other workers (43).

C. Effects on the Liver and Carbohydrate Metabolism

Early studies indicate that acute exposure to cadmium oxide fumes alters liver function. Autopsies have revealed microscopic changes in the liver, but these were slight compared to other acute effects (7).

The evidence suggests that workers chronically exposed to cadmium have impaired liver function (7). However, effects on the liver have not been examined as extensively as those on other organs.

Cadmium given intraperitoneally to rats, either 1.0 mg/kg or 0.25 mg/kg every second day for 40 days, altered the glucose metabolic activity (58). Cadmium fed to rats, 1.0 mg/kg/day for 60 days, produced a statistically significant decrease in phosphorylase A enzyme activity. The same dosage resulted in a substantial decrease in the Pi/O ratio, suggesting an uncoupling of oxidative phosphorylation. In addition, a dose of 0.1 mg/kg/day for 42 days resulted in a signficant decrease in aldolase activity (59). Insulin levels were significantly decreased in rats given seventy doses of 0.5 mg/kg cadmium every second day, whereas a 0.25 mg/kg dose did not produce these effects (58). In another study additional enzyme activities including ascorbic acid synthesis were altered in rats fed a dose of 60 mg/kg for four weeks (60).

D. Effects on Cardiovascular System

Cadmium in acutely toxic amounts increases the blood pressure in many rodent species (7), but there are no reports of this effect in exposed humans. However, epidemiologic evidence indicates that hypertension is less prevalent in areas of the world where the total body burden of cadmium is less (68).

Chronic human exposure has been epidemiologically linked to hypertension in some reports, but this is an area of some disagreement (7). Animal studies clearly indicate that hypertension is produced by cadmium given orally or by injection (1,7). Rats given cadmium (5 ppm or 10 ppm for life) in their drinking water developed hypertension (62). Cadmium (5 ppm in drinking water) administered for the life of the animal induced arteriosclerosis by reducing the amount of circulating cholesterol (63).

E. Effects on the Gonads

When testicles were injected subcutaneously with cadmium (2.24 mg/kg), microscopic changes were evident within a few hours. Capillary stasis and interstitial edema were followed by severe hemorrhage and necrosis 24 to 48 hours later (7). Necrosis was dose-dependent and reversible.

Testicular necrosis also occurred when cadmium (28 and 64 mg/kg) was administered in food, painted on the skin, or injected intravenously or intraperitoneally (7). In a recent study, treatment with an amount of cadmium that produces general toxic effects (3 mg/kg in drinking water) also produced gonadotoxic effects including membrane thickening, hypertrophy and proliferation of Sertoli cells, and swelling of arteriolar walls (61). The lowest single subcutaneous dose which has produced acute testicular necrosis in the most sensitive laboratory animals, certain strains of mice, is 1 mg/kg (7).

Chronic effects on the gonads have been induced in animals fed cadmium or given repeated subcutaneous injections of cadmium. However no testicular necrosis has been reported in humans industrially exposed to cadmium (1,7).

F. Effects on the Skeleton

Cadmium is not known to accumulate in bone and correspondingly does not appear to have any acute effect upon the skeleton (67). However, cadmium apparently affects the metabolism of calcium and phosphorus. Itai-Itai disease, probably the most insidious result of chronic exposure to cadmium in the food and water, is thought to have resulted from combined effects of interference of calcium and phosphous metabolism by cadmium, vitamin-D deficiency, and a low protein diet. Low protein diets deficient in vitamin D are typical of Toyama Prefecture, Japan, the only area in which the disease has been found. Pseudo-fractures and decalcification have been found in humans exposed to cadmium for up to 20 years (1,7).

Cadmium (5 and 10 ppm given in water for 50 days) causes tooth discoloration in rats (64). Bone disorders, in particular decalcification, develop in animals fed 1 to 2 mg/kg in food for 120 days (65).

G. Effects on the Hematopoietic System

Elevated hemoglobin concentrations are the only hematopoietic abnormality caused by acute exposure to

cadmium. However, the edema that appeared concurrently may have been the primary result of exposure to cadmium, the elevated hemoglobin being only a consequence of the edema (7).

Chronic exposure to small quantities of cadmium has been linked epidemiologically to decreased hemoglobin levels. White cell counts have been found to be essentially normal, with the exception of an increase in the number of eosinophiles. Bone marrow in all of these surveys showed no pathological changes (7).

Animals treated with cadmium have been shown to develop anemia and lowered hemoglobin levels. Dosages as low as 2.0 mg/kg fed to rats for four months have produced these effects. However, these effects can be mitigated by the simultaneous increase of additional iron to the diet. Dose response levels have been determined in rats given injections of cadmium, but no dose-response levels have been determined in studies using other routes of exposure with levels ranging from 0.5 to 10 ug/g for up to one year (7).

H. Effects on the Central Nervous System

Chronic cadmium exposure produced headache and vertigo in one human (7). Physical examination revealed that he had altered neuromuscular reflexes. Olfactory disturbances, anosmia, and hyposmia, were found to be common in a worker population, 50% of which had been exposed for at least 10 years at concentrations of 3 to 15 mg/m^3 (1).

Cadmium injected intraperitoneally (0.25 and 1.0 mg/kg/day) for 45 days accumulated in the rat brain and acted on several indicators of brain activity such as the concentration or norepinephrine, acetylcholine, and 5-hydrotryptamine (66).

List of Appendices

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